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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/842,234	04/26/2001	Kiyoshi Nakayama	P20938	7436

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EXAMINER	
RAO, DEEPAK R	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 06/16/2004

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/842,234	NAKAYAMA ET AL.	
	Examiner	Art Unit	
	Deepak R Rao	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18,20,22 and 24-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1-3 and 5* is/are allowed.

6)☒ Claim(s) *4,6-18,20,22 and 24-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *18*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after allowance or after an Office action under *Ex Parte Quayle*, 25 USPQ 74, 453 O.G. 213 (Comm'r Pat. 1935). Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission (supplemental Information Disclosure Statement) filed on March 5, 2004 has been entered.

Claims 1-18, 20, 22 and 24-32 are pending in this application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 4, 6, 7-18, 20, 22 and 24-27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for therapeutic treatment of a microbial infection due to *Pseudomonas aeruginosa*, does not reasonably provide enablement for therapeutic and/or preventive treatment of microbial infections due to other microorganisms. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed. The determination that "undue experimentation" would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the above noted factual considerations.

Claims 4, 6 and 20 are drawn to a composition which is used for "preventive and/or therapeutic treatment" of microbial infection generally. No compound has ever been found that can treat infectious disorders generally. Since this assertion is contrary to what is known in medicine, proof must be provided that this revolutionary assertion has merits. Nearly all drugs for treating infections are effective against only a limited group of disorders. Therefore, a compound effective against disorders of the neuronal system generally would be a revolutionary exception. It is well established that an enablement rejection is proper when the scope of enablement is not reasonably correlated to the scope of the claims. (*In re Vaeck*, 20 USPQ2d 1439, 1444 (CAFC 1991); *In re Ferens*, 163 USPQ 609).

It is inconceivable as to how the claimed compounds can treat or prevent all types of microbial infections for which applicants provide no competent evidence. For example, there is no common mechanism by which all microbial infectious conditions arise. Accordingly, treatments for these diseases are normally tailored to the particular type of microorganism or infection present and there is no "magic bullet" against infections in general. There is no

evidence of record which would enable the skilled artisan in the identification of the people who have the potential of becoming afflicted with the disease(s) or disorder(s) due to such infections. The only test assay in the specification provides data for a specific microorganism *Pseudomonas aeruginosa.*

There is no evidence in the record which demonstrates that the screening tests relied upon are recognized in the art as being reasonably predictive of success in any of the contemplated areas of 'therapeutic treatment' and 'preventive treatment' of all types of microbial infections. Such a reasonable correlation is necessary to demonstrate such utilities. See *Ex parte Stevens*, 16 USPQ 2d 1379 (BPAI 1990); *Ex parte Busse* et al., 1 USPQ 2d 1908 (BPAI 1986) (the evidence must be accepted as "showing" such utility and not "warranting further study"). The evidence presented in this case does not show such utilities, but only warrants further study.

Furthermore, the scope of the claims is not adequately enabled solely based on the antimicrobial activity provided in the specification. The instant claims are drawn in part to preventive treatment, which is not remotely enabled. The instant compounds are disclosed have antimicrobial activity and it is recited that the instant composition is useful in the "prevention" of microbial infections, etc., for which applicants provide no competent evidence. "To prevent" actually means *to anticipate* or *counter in advance, to keep from happening etc.* (as per Websters II Dictionary) and therefore it is not understood how one skilled in the art can reasonably establish the basis and the type of subject to which the instant compounds can be administered in order to have the "preventive" effect. There is no evidence of record which would enable the skilled artisan in the identification of the people who have the potential of becoming afflicted with the disease or disorder claimed herein.

1) The nature of the invention: The method of use claims are drawn to therapeutic and preventive treatment of any and all microbial infections, etc. Currently, there are no known agents with the chemotherapeutic efficacy to prevent microbial infections generally. The art does not disclose an active agent or combination of active agents which is recognized to prevent the conditions cited supra. The prior art does not teach or disclose a treatment modality wherein healthy subjects are administered an active agent or agent(s) and there is evidence that none of the associated symptoms or disease state characteristics are ever manifested. The disclosure does not direct the skilled artisan to art which satisfies the requirement for preventing a disease state associated with endothelial dysfunction selected from the group consisting of arteriosclerosis, diabetes, infections, inflammation, stroke and cardiovascular disease.

2) The state of the prior art: There are no known compounds of similar structure which have been demonstrated to treat or prevent all of the diseases due to microbial infections. Some of the state of the art reference statements are provided below to show the unpredictability of the art:

Saadia (BMJ 1997): "With so many variables, the diagnosis of candida infection in practice remains a clinical decision based on inference. Disseminated fungal infection may be diagnosed with certainty if a patient develops endophthalmitis or a positive fungal culture is made from an organ such as the kidney or lung. However, the number of positive blood cultures or number of colonised sites required for such a diagnosis remains uncertain."

Satcher (Emerging Infectious Diseases1995): "we must be ever mindful of the cyclical nature of disease trends". "Clearly, the complete history of infectious diseases remains to be written".

Molinari (1999): "The emergence of increasingly resistant microorganisms requires constant vigilance on the part of health care professionals with regard to utilizing alternative antimicrobial

treatment approaches. As the number of hospitalized patients and outpatients presenting with infections containing drug-resistant strains rises, careful identification of etiologic organisms and their sensitivity profiles will continue to take on increased importance in ensuring successful treatment. What was once thought primarily to be a medical issue in hospitals has gradually involved more oral surgeons, periodontists, endodontists, and other dentists. In addition to symptomatic infections, affected patients may become colonized as short-or long-term carriers of strains of multiple-drug-resistant *S. aureus* or other potentially dangerous pathogens. It should also be remembered that colonization is much more common than clinical infection and also more difficult to eliminate. Judicious use of antibiotics only when needed and strict adherence to routinely effective infection control practices have been shown to reverse some of the described trends, and these approaches need to be expanded."

3) The predictability or lack thereof in the art: It is presumed in the prevention of the diseases and/or disorders claimed herein there is a way of identifying those people who may develop any kind of the infection. There is no evidence of record which would enable the skilled artisan in the identification of the people who have the potential of becoming afflicted with the infections intended herein. Applicants have not provided any competent evidence or disclosed tests that are highly predictive for all the instantly claimed preventive treatment. Therapeutic treatment of microbial infections depends on many differing effects of factors such as endemic pathogens, underlying diseases, and antimicrobial prescribing habits.

4) The amount of direction or guidance present and 5) the presence or absence of working examples: There are no doses present to direct one to protect a potential host from the microbial infections and there is no data present for the preventive effect of the treatment. The examiner

notes, there is not seen sufficient guidance provided in the form of administration profiles, combination ratios of the active agents or references to same in the prior art to provide the skilled artisan with sufficient guidance to practice the instant method of therapeutic or preventive treatment. Particularly, **preventive** treatment is seen to encompass administering the active agent to a baby or small child or healthy adult, and noting the fact that symptoms of the microbial infections never manifest themselves. The data and evidence provided in the instant disclosure leads the examiner to doubt the objective truth of assertions of prevention of the microbial infections of the claims. Many microorganisms have mechanisms that impair antibody production at different sites by inducing suppressor cells, blocking antigen processing, and inhibiting lymphocyte mitogenesis.

A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). There is not seen in the disclosure, sufficient evidence to support applicant's claims of therapeutic and preventive treatment of all types of microbial infections. The Test Examples 1-3 in pages 169-170 and 175-177 all relate to 'Effect of combined use of antimicrobial agent or drug efflux pump inhibitor along with the compound of the invention'. There is not seen sufficient working examples or data from references of the prior art providing a nexus between that which applicant asserts as proof of a method for treating and preventing microbial infections or extrapolation from the data and evidence currently provided on the record to support methods drawn to preventing any such conditions.

6) The breadth of the claims: The claims are drawn to therapeutic and preventive treatment of all microbial infectious disorders that are not related and whose prevention of all microbial infections generally is unknown.

7) The quantity of experimentation needed would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan, regarding therapeutic and preventive treatment of all disorders due to microbial infection.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method claims. In view of the breadth of the claim, the chemical nature of the invention, the unpredictability of ligand-receptor interactions in general, and the lack of working examples regarding the activity of the claimed compounds, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the instantly claimed invention commensurate in scope with the claims.

The discussion in the Background of the invention disclosed in the specification and the arguments provided in paper no. 8 and 14 have been fully considered but they were not deemed sufficient to overcome the rejection.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 28-32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as

the invention. The claims do not recite "in need of" following 'mammal'. Appropriate amendment would obviate the rejection.

Allowable Subject Matter

Claims 1, 2, 3 and 5 are allowed. The references of record do not teach or fairly suggest the claimed compounds. Claims 32-33 would be allowable if rewritten or amended to overcome the rejection(s) under 35 U.S.C. 112, second paragraph, set forth in this Office action. Claims 28-31 would be allowable if rewritten to overcome the rejection(s) under 35 U.S.C. 112, second paragraph, set forth in this Office action and to include all of the limitations of the base claim and any intervening claims.

The Information Disclosure Statement filed on March 5, 2004 is acknowledged and a copy is enclosed herewith.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deepak Rao whose telephone number is (571) 272-0672. The examiner can normally be reached on Tuesday-Friday from 6:30am to 5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Mukund Shah, can be reached on (571) 262-0674. If you are unable to reach Dr. Shah within a 24 hour period, please contact James O. Wilson, Acting-SPE of 1624 at (571) 272-

0661. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Deepak Rao
Primary Examiner
Art Unit 1624

June 12, 2004